ClinicalEvidence

Leprosy

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ABSTRACT

INTRODUCTION: The World Health Organization field leprosy classification is based on the number of skin lesions: single-lesion leprosy (1 lesion), paucibacillary leprosy (2–5 skin lesions), and multibacillary leprosy (more than 5 skin lesions). Worldwide, about 720,000 new cases of leprosy are reported each year, and about 2 million people have leprosy-related disabilities. METHODS AND OUTCOMES: We conducted a systematic review and aimed to answer the following clinical questions: What are the effects of interventions to prevent leprosy? What are the effects of treatments for leprosy? We searched: Medline, Embase, The Cochrane Library and other important databases up to March 2006 (BMJ Clinical Evidence reviews are updated periodically, please check our website for the most up-to-date version of this review). We included harms alerts from relevant organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA). RESULTS: We found 20 systematic reviews, RCTs, or observational studies that met our inclusion criteria. We performed a GRADE evaluation of the quality of evidence for interventions. CONCLUSIONS: In this systematic review we present information relating to the effectiveness and safety of the following interventions: Bacillus Calmette Guerin (BCG) plus killed Mycobacterium leprae vaccine; BCG vaccine; ICRC vaccine; multidrug treatment; multiple-dose treatment; mycobacterium w vaccine; single-dose treatment.

QUESTIONS

INTERVENTIONS

PREVENTION OF LEPROSY

Beneficial

Likely to be beneficial

Unlikely to be beneficial

TREATMENTS FOR LEPROSY

Beneficial

To be covered in future updates

Treatment of reactions

Footnote

*Categorisation based on observational evidence and consensus; RCTs unlikely to be conducted.

Key points

- Leprosy is a chronic granulomatous disease caused by *Mycobacterium leprae*, primarily affecting the peripheral nerves and skin.

  The World Health Organization field leprosy classification is based on the number of skin lesions: single lesion leprosy (1 lesion), paucibacillary leprosy (2–5 skin lesions), and multibacillary leprosy (> 5 skin lesions).

  Worldwide, about 720 000 new cases of leprosy are reported each year, and about 2 million people have leprosy related disabilities.

- Vaccination is the most efficient method of preventing the contraction of leprosy.

  Bacillus Calmette Guerin (BCG) vaccination reduces the incidence of leprosy, although we don't know for sure if Bacillus Calmette Guerin (BCG) vaccination plus killed M leprae improves its effectiveness.

  ICRC vaccine prevents leprosy and produces few adverse effects, although its formulation is unclear and we only found evidence in one geographical area.

  Mycobacterium w vaccine reduces the incidence of leprosy compared with placebo, but is less effective than ICRC or BCG (alone or with killed *M leprae*).

- Leprosy is generally treated with multidrug programmes.

  Despite sparse good RCT or cohort study evidence, there is consensus that multidrug treatment (rifampicin plus clofazimine plus dapsone) is highly effective for treating multibacillary leprosy.

Multidrug treatment with rifampicin plus dapsone is believed to improve skin lesions, nerve impairment, and relapse rates in people with paucibacillary leprosy, despite a lack of good evidence.

Multiple dose treatments with rifampicin monthly plus dapsone daily for 6 months are more effective than single dose treatments with rifampicin plus minocycline plus ofloxacin for treating people with single skin lesions (although both achieve high cure rates).

DEFINITION

Leprosy is a chronic granulomatous disease caused by *Mycobacterium leprae*, primarily affecting the peripheral nerves and skin. The clinical picture depends on the individual's immune response to *M leprae*. At the tuberculoid end of the Ridley–Jopling scale, individuals have good cell mediated immunity and few skin lesions. At the lepromatous end of the scale, individuals have low reactivity for *M leprae*, causing uncontrolled bacterial spread and skin and mucosal infiltration. Peripheral nerve damage occurs across the spectrum. Nerve damage may occur before, during, or after treatment. Some people have no nerve damage, while others develop anaesthesia of the hands and feet, which puts them at risk of developing neuropathic injury. Weakness and paralysis of the small muscles of the hands, feet, and eyes puts people at risk of developing deformity and contractures. Loss of the fingers and toes is caused by to repeated injury in a weak, anaesthetic limb. These visible deformities cause stigmatisation. Classification is based on clinical appearance and bacterial index of lesions. The World Health Organization field leprosy classification is based on the number of skin lesions: single lesion leprosy (1 lesion), paucibacillary leprosy (2–5 skin lesions), and multibacillary leprosy (> 5 skin lesions). [1]

INCIDENCE/ PREVALENCE

Worldwide, about 720 000 new cases of leprosy are reported each year, [2] and about 2 million people have leprosy related disabilities. Six major endemic countries (India, Brazil, Myanmar, Madagascar, Nepal, and Mozambique) account for 88% of all new cases. Cohort studies show a peak of disease presentation between 10 and 20 years of age. [3] After puberty, there are twice as many cases in males as in females.

AETIOLOGY/ RISK FACTORS

M leprae is discharged from the nasal mucosa of people with untreated lepromatous leprosy, and spreads, via the recipient's nasal mucosa, to infect their skin and nerves. It is a hardy organism and has been shown to survive outside human hosts in India for many months. [4] Risk factors for infection, when known, include household contact with a person with leprosy. We found no good evidence of an association with HIV infection, nutrition, or socioeconomic status. [5] [6] [7]

PROGNOSIS

Complications of leprosy include nerve damage, immunological reactions, and bacillary infiltration. Without treatment, tuberculoid infection eventually resolves spontaneously. Most people with borderline tuberculoid and borderline lepromatous leprosy gradually develop lepromatous infection. Many people have peripheral nerve damage at the time of diagnosis, ranging from 15% in Bangladesh [8] to 55% in Ethiopia. [9] Immunological reactions can occur with or without antibiotic treatment. Further nerve damage occurs through immune-mediated reactions (type 1 reactions) and neuritis. Erythema nodosum leprosum (type 2 reactions) is an immune complex mediated reaction causing fever, malaise, and neuritis, which occurs in 20% of people with lepromatous leprosy, and 5% with borderline lepromatous leprosy. [10] Secondary impairments (wounds, contractures, and digit resorption) occur in 33–56% of people with established nerve damage. [11] We found no recent information on mortality.

AIMS OF INTERVENTION

Prevention: To prevent infection. **Treatment:** To treat infection and improve skin lesions; to prevent relapse and complications (nerve damage and erythema nodosum leprosum). Prevention of complications such as ulcers and deformity may improve the quality of life for the individual and help reduce the severe stigmatisation that still accompanies leprosy.

OUTCOMES

Prevention: Incidence of leprosy. **Treatment:** Clinical improvement, relapse rate, quality of life, adverse effects of treatment, and mortality.

METHODS

BMJ Clinical Evidence search and appraisal March 2006. Additional searches were carried out on the NHS Centre for Reviews and Dissemination (CRD), Database of Abstracts of Reviews of Effects (DARE), Health Technology Assessment (HTA), Turning Research into Practice (TRIP), and the National Institute for Health and Clinical Excellence (NICE) websites. Abstracts of studies retrieved in the search were assessed independently by two information specialists. Predetermined criteria were used to identify relevant studies. Study design criteria included: systematic reviews and RCTs. For inclusion, studies had to be at least single blind. We excluded all studies described as “open”, “open label” or non-blinded. The minimum number of individuals in each trial was 20. Size of follow up was 80% or more. There was no minimum length of follow up. We also did a search for cohort studies for relevant questions and looked for case series from 1990 onwards for some options. Additional studies were also identified by hand searches of reference lists by the author and contact

with experts in the field.We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 13).

QUESTION What are the effects of interventions to prevent leprosy?

OPTION BACILLUS CALMETTE GUERIN VACCINE

Mortality
Compared with placebo Bacillus Calmette Guerin (BCG) vaccine may reduce all-cause mortality compared with placebo (very low-quality evidence).

Incidence of leprosy
BCG compared with placebo BCG vaccine alone may reduce the incidence of leprosy after 5–16 years' follow-up compared with placebo (low-quality evidence).

BCG plus M leprae vaccine compared with placebo Combined vaccination with BCG and M leprae reduces the incidence of leprosy compared with placebo (high-quality evidence).

ICRC vaccine compared with placebo ICRC vaccine reduces the incidence of leprosy compared with placebo (high-quality evidence).

Mycobacterium w vaccine compared with placebo Mycobacterium w vaccine reduces the incidence of leprosy compared with placebo (high-quality evidence).

BCG plus M leprae vaccine compared with BCG alone Combined vaccination with BCG plus M leprae may be no more effective at reducing the incidence of leprosy than BCG vaccine alone (low-quality evidence).

Higher-dose BCG vaccine compared with lower-dose BCG vaccine It is unclear whether a higher concentration of BCG vaccine reduces the incidence of leprosy compared with a lower dose (very low-quality evidence).

Adverse effects
BCG vaccine alone is associated with minimal adverse effects.

For GRADE evaluation of interventions for leprosy, see table, p 13 .

Benefits:

Bacillus Calmette Guerin versus no treatment or placebo:
We found one systematic review (search date 2005), which included experimental studies (1 randomised and 6 non-randomised controlled trials) and observational studies (19 cohort and case control studies). [12] Meta-analysis of the experimental studies (including the RCT presented below [13]) found an overall protective effect associated with Bacillus Calmette Guerin (BCG) vaccine after 5–16 years' follow up (7 studies; RRR 26%, 95% CI 14% to 37%). Meta-analysis of the observational studies also found an overall protective effect associated with BCG vaccine at 4–5 years' follow up (19 studies; RRR 61%, 95% CI 51% to 70%). The authors of the review noted that the meta-analysis of observational studies overestimated the protective effect of BCG. The reason for the higher protective efficacy in the observational studies might be that the observational studies had a shorter period of follow up compared with the experimental studies, and protective efficacy seems to decrease with time. One of the trials included in the meta-analysis of experimental studies also looked at mortality, and found a significant reduction (deaths from all causes: 442/2707 [16.3%] with BCG *v* 489/2649 [18.5%] with saline; RR 0.89, 95% CI 0.79 to 0.99; NNT 47, 95% CI 24 to 997). [14] The systematic review evaluating the effectiveness of BCG found there was heterogeneity between studies in both meta-analyses. [12]

Bacillus Calmette Guerin plus killed Mycobacterium leprae versus placebo or Bacillus Calmette Guerin alone:
We found one RCT carried out in Malawi with clinical leprosy as the outcome measure (see table 1, p 10). [15] The RCT stratified people according to the presence of a BCG scar. Those with a scar or a possible scar (54 865 people) received either BCG, BCG plus killed *M leprae*, or placebo. This RCT found that combined results for BCG and BCG plus killed *M leprae* indicated significantly reduced incidence of leprosy compared with placebo. Those without a scar (66 155 people) received BCG or BCG plus killed *M leprae*. The RCT found no significant difference between the two vaccines.

Bacillus Calmette Guerin (BCG), BCG plus killed *M leprae* , ICRC vaccine, or *Mycobacterium w* vaccine versus placebo:
We found one RCT, carried out in a leprosy endemic area with clinical leprosy as the outcome measure (see table 1, p 10). [13] The RCT (double blind, 171 400 healthy people in India aged 1–65 years, follow up for 6–7 years) compared four vaccines (BCG: 38 213 people; BCG plus killed

M leprae: 38 229 people; ICRC vaccine: 22 541 people; and *Mycobacterium w* vaccine: 33 720 people) versus normal saline (38 697 people). It included a statistical adjustment for the multiple comparisons against saline. All four vaccines significantly reduced the incidence of leprosy compared with saline. The most effective vaccines were ICRC vaccine (RRR 65.5%, 95% CI 48.0% to 77.0%) and BCG plus killed *M leprae* (RRR 64.0%, 95% CI 50.4% to 73.9%). BCG alone was also effective (RRR 34.1%, 95% CI 13.5% to 49.8%), whereas the significance of the effect of *Mycobacterium w* was marginal (RRR 25.7%, 95% CI 1.9% to 43.8%).

BCG at different doses versus placebo:
A controlled clinical trial performed in Myanmar compared two different concentrations of BCG vaccine versus no treatment. [16] The vaccine with the higher concentration of bacilli significantly reduced the incidence of leprosy over 14 years (3.8/1000 person years with BCG *v* 5.4/1000 person years with control; RRR 30%, 95% CI 19% to 40%). The vaccine with the lower concentration of bacilli had no significant protective effect (5.0/1000 person years with BCG *v* 5.6/1000 person years with control; RRR +11%, 95% CI –3% to +23%). The RCT performed in Malawi found no significant differences between a higher and a standard dose of killed *M leprae*. [15]

Harms: The review [12] and other trials [14] [15] [16] identified by the review did not report on adverse effects.

Bacillus Calmette Guerin (BCG), BCG plus killed *M leprae* , ICRC vaccine, or *Mycobacterium w* vaccine versus placebo:
The RCT conducted in India found that "fluctuant adenitis" was minimal with all four vaccines used, and no other adverse effects were observed (numbers not reported). [13]

Comment: In the trial in Malawi, 7/82 (9%) people tested positive for HIV. [15] Eleven different batches of BCG were used. The number of people lost to follow up was high (26%), and the sample size may have been insufficient to rule out clinically important effects, given that there were multiple comparisons against placebo.

OPTION BACILLUS CALMETTE GUERIN PLUS KILLED MYCOBACTERIUM LEPRAE VACCINE

Incidence of leprosy
Bacillus Calmette Guerin (BCG) plus M leprae vaccine compared with placebo Combined vaccination with BCG and M leprae reduces the incidence of leprosy compared with placebo at 5–9 years' follow-up (high-quality evidence).

Adverse effects
BCG vaccine plus killed M leprae is associated with minimal adverse effects .

For GRADE evaluation of interventions for leprosy, see table, p 13 .

Benefits: See benefits of Bacillus Calmette Guerin vaccine, p 3 .

Harms: See harms of Bacillus Calmette Guerin vaccine, p 3 .

Comment: None.

OPTION ICRC VACCINE

Incidence of leprosy
ICRC vaccine compared with placebo ICRC vaccine reduces the incidence of leprosy compared with placebo at 6–7 years' follow-up, with greater efficacy compared with Bacillus Calmette Guerin (BCG) plus killed Mycobacterium leprae, BCG alone, and Mycobacterium w vaccines (high-quality evidence).

Adverse effects
The ICRC vaccine is associated with minimal adverse effects. The formulation of ICRC vaccine is unclear, and we only found evidence in one geographical region.

For GRADE evaluation of interventions for leprosy, see table, p 13 .

Benefits: See benefits of Bacillus Calmette Guerin vaccine, p 3 .

Harms: See harms of Bacillus Calmette Guerin vaccine, p 3 .

Comment: **Clinical guide:**
We only found evidence of ICRC vaccine in one region with leprosy (India). The formulation of the vaccine is unclear.

OPTION MYCOBACTERIUM W VACCINE

Incidence of leprosy
Mycobacterium w vaccine compared with placebo Mycobacterium w vaccine reduces the incidence of leprosy compared with placebo after 9 years' follow-up (high-quality evidence). Mycobacterium w is less effective than ICRC vaccine, Bacillus Calmette Guerin (BCG) plus killed Mycobacterium leprae, and BCG alone at reducing leprosy infection rates, but can be effective when given to household contacts of people with leprosy alone, or to both the people with leprosy and their contacts, compared with placebo.

Adverse effects
Mycobacterium w vaccine is associated with minimal adverse effects.

For GRADE evaluation of interventions for leprosy, **see table, p 13** **.**

Benefits:

***Mycobacterium w* vaccine versus placebo:**
One cluster RCT (randomisation by village, 272 villages stratified by size and leprosy prevalence; 29 420 household contacts assessed) compared four different vaccination strategies for people with leprosy and their household contacts: patient and contacts both vaccinated, only patient vaccinated, only contacts vaccinated, and placebo for both patient and contacts. [17] It found that *Mycobacterium w* vaccination of patients and contacts or contacts alone had a protective effect compared with placebo at up to 9 years (see table 1, p 10). Vaccination of leprosy patients only had a lower protective efficacy than the other vaccination strategies, and was not significantly different from placebo at 9 years (see table 1, p 10).See also benefits of Bacillus Calmette Guerin vaccine, p 3 .

Harms:

The cluster RCT comparing *Mycobacterium w* vaccination versus placebo found that there were no major adverse effects, although there were some cases of injection site induration and ulceration. [17] See also harms of Bacillus Calmette Guerin vaccine, p 3 .

Comment:

None.

QUESTION What are the effects of treatments for leprosy?

OPTION MULTIDRUG TREATMENT FOR MULTIBACILLARY LEPROSY

We found no direct information about whether multidrug treatment is better than no active treatment in multibacillary leprosy. We found no clinically important results about the effects of multidrug treatment with rifampicin plus clofazimine plus dapsone compared with dapsone plus rifampicin, or dapsone alone in multibacillary leprosy.

Adverse effects
The incidence of adverse effects with multidrug treatment is unclear.

For GRADE evaluation of interventions for leprosy, **see table, p 13** **.**

Benefits:

We found no systematic review, RCTs, cohort studies with comparators, or case control studies. We found six case series assessing the effects of multidrug treatment (monthly supervised rifampicin 600 mg and clofazimine 300 mg, plus daily unsupervised dapsone 100 mg and clofazimine 500 mg) for 24 months. [18] [19] [20] [21] [22] [23]

Skin lesions:
One study in Thailand (53 people) found that 29% of lesions were still active at 3 years (see table 2, p 11). [18]

Nerve impairment:
The study in Thailand found that the proportion of people with visible deformity (World Health Organization grade II) increased from 8% at enrolment to 13% at 8–10 years of follow up. [18]

Relapse:
Seven case series reported relapse rates (see table 2, p 11), [18] [19] [20] [21] [22] [23] which varied from 0/1000 person years in Ethiopia to 20.4/1000 person years in India. In the study conducted in India which had the highest relapse rate, the overall relapse rate was 20/260 (7.7%) over about 8 years (20.4/1000 person years), and 18/20 (90%) relapses were in people with a bacterial index greater than 4 at the start of treatment. [22] Relapse is generally defined as a person successfully completing multidrug treatment, but subsequently developing signs or symptoms of leprosy either during a surveillance period or afterwards. [24]

Harms: Most case series did not report on adverse effects. Skin pigmentation may occur with clofazimine, which may be especially problematic in people with fair skin.

Comment: We found one RCT (93 people with untreated lepromatous leprosy), which compared dapsone 50 mg daily plus rifampicin 450 mg daily versus dapsone 50 mg daily plus rifampicin 1200 mg monthly for the first 6 months of treatment. [22] It found no significant difference in clinical improvement between daily and monthly rifampicin (40/47 [85%] with daily rifampicin *v* 43/46 [91%] with monthly rifampicin; RR 0.91, 95% CI 0.62 to 1.03). Adverse effects were more common with daily than with monthly rifampicin, causing discontinuation in 8.5% of people with daily rifampicin compared with 0% with monthly rifampicin. [25]

Clinical guide:
Evidence from cases series of clinical improvement and relapse rates suggests that dapsone plus clofazimine plus rifampicin is effective for treating multibacillary leprosy, and studies comparing multidrug treatment versus placebo or no treatment would now be considered unethical. Multidrug treatment was not compared with dapsone alone because rising dapsone resistance rates would make such a study unethical. Only one case series stratified results according to bacterial index. [22] The World Health Organization study group on chemotherapy recommended that treatment be given for 24 months. [26] In 1998, the 7th Expert Committee gave the option of reducing the length of treatment from 24 months to 12 months. [1] We found no controlled trial to support this recommendation.

OPTION MULTIDRUG TREATMENT FOR PAUCIBACILLARY LEPROSY

We found no direct information about whether multidrug treatment is better than no active treatment in people with paucibacillary leprosy. We found no clinically important results about the effect of multidrug treatment with rifampicin plus dapsone compared with dapsone alone in paucibacillary leprosy.

Adverse effects
The incidence of adverse effects with multidrug treatment is unclear.

For GRADE evaluation of interventions for leprosy, **see table, p 13** **.**

Benefits: We found no systematic review, RCTs, cohort studies with comparators, or case control studies (see comment below). We found seven case series assessing the effects of multidrug treatment (dapsone 100 mg/day plus rifampicin 600 mg monthly for 6 months), with follow up ranging from 6 months to 10 years (see table 3, p 12). [18] [19] [20] [21] [27] [28] [29] [30] The studies used different methods of assessment, making it difficult to compare results.

Skin lesions:
Three case series reported rates of resolution of skin lesions (see comment below) (see table 3, p 12). [18] [27] [28] [29] One study (499 people) found that resolution of lesions occurred in 38% of people after 1 year; [28] another (50 people) found that resolution occurred in 8% of people after 6 months. [27] The number of people with lesions that were clinically active after treatment ranged from 2% to 44%. [18] [27] [28]

Nerve impairment:
Two case series reported rates of new or worsening nerve impairment (see table 3, p 12). [18] [29] One study (499 people) found that new disabilities occurred in 2.5% of people, and worsening of existing disabilities occurred in 3.3% after 4 years. [29] The other study (130 people) found that the visible disabilities (World Health Organization grade II) increased from 4% at enrolment to 7% after 8–10 years of follow up. [18]

Relapse:
Six case series reported relapse rates over a 3–8 year follow up period (see table 3, p 12). [18] [19] [20] [21] [29] [30] The risk of relapse ranged from 0% over a mean of 4.1 years in Ethiopia [19] and 0.33% over 5 years (0.66/1000 person years) in China [21] to 2.5% over 4 years (6.5/1000 person years) in Malawi. [29] (It is clinically difficult to differentiate relapse from reaction in paucibacillary leprosy.)

Harms: None of the case series formally monitored adverse effects. In one study, hepatitis due to rifampicin occurred in 1/130 people (0.8%), but the method of diagnosis was not reported. [18] In another study, 1/503 people (0.2%) suffered an “allergic reaction” to rifampicin and dapsone (details not reported). [28]

Comment: **Clinical guide**:
In 1982, studies had shown that 30% of *Mycobacterium leprae* isolates were resistant to dapsone. [31] Therefore, the World Health Organization introduced the combination of dapsone plus rifampicin urgently, without formal RCTs comparing it against dapsone, and such studies would now be considered unethical. Studies comparing multidrug treatment versus placebo or no treatment would also be considered unethical because of consensus regarding efficacy of multidrug treatment.

OPTION MULTIPLE DOSE VERSUS SINGLE DOSE TREATMENT FOR SINGLE SKIN LESIONS

Clinical improvement
Multiple-dose treatment compared with single-dose treatment Multiple-dose treatment with rifampicin monthly plus dapsone daily for 6 months may achieve higher clinical improvement rates at 18 months compared with single-dose treatment with rifampicin plus minocycline plus ofloxacin (low-quality evidence).

Adverse effects
Adverse effects are similar with both regimens.

For GRADE evaluation of interventions for leprosy, **see table, p 13** **.**

Benefits: We found no systematic review. We found one RCT (1483 people with single skin lesions typical of paucibacillary leprosy; see comment below) comparing single dose treatment with rifampicin 600 mg plus ofloxacin 400 mg plus minocycline 100 mg versus multiple dose treatment with dapsone 100 mg daily plus rifampicin 600 mg monthly for 6 months. [32] Outcomes measured at 18 months were based on a scoring system involving five measurements: disappearance of the lesion, reduction in hypopigmentation, reduction in the degree of infiltration, reduction in the size of the lesion, and improvement in sensation in the lesion. Treatment failure was defined as no change or an increase in the clinical score; and marked improvement was defined as a difference of 13 between the baseline and 18 month scores. The RCT found that multiple dose treatment significantly increased the proportion of people with marked improvement compared with single dose treatment (392/684 [57.3%] with multiple dose *v* 361/697 [51.8%] with single dose; P = 0.04) and with complete cure (assessed clinically; 374/684 [54.7%] with multiple dose *v* 327/697 [46.9%] with single dose; RR 1.17, 95% CI 1.05 to 1.28; NNT 13, 95% CI 8 to 40). There were 12 treatment failures (6 in each group), and 99.1% of people in both groups had some improvement by the end of the study. [32]

Harms: Allergic reactions (which were not specified) occurred in seven people (6 with multiple dose *v* 1 with single dose), and gastrointestinal effects occurred in five people (2 with multiple dose *v* 3 with single dose). There was no significant difference in the number of type 1 reactions (3/684 [0.4%] with multiple dose *v* 7/697 [1.0%] with single dose; ARI +0.6%, 95% CI –0.2% to +3.4%).

Comment: The RCT did not specify its diagnostic criteria and did not confirm the clinical diagnosis. The follow up of only 18 months for people in the single dose group is short for detection of relapse. Some infections in this group would have resolved spontaneously, and the absence of a placebo control group means that the treatment effect cannot be estimated. [32] Single dose treatment has previously been assessed in people with paucibacillary leprosy. One RCT (622 people in Zaïre) compared two single dose regimens: rifampicin 40 mg/kg plus clofazimine 1200 mg versus rifampicin 40 mg/kg plus clofazimine 100 mg plus dapsone 100 mg plus ethionamide 500 mg. It found that the overall relapse rate was 20.4/1000 person years, which was substantially higher than the relapse rate found for 6 months of treatment with dapsone plus rifampicin (see comment on multidrug treatment for paucibacillary leprosy, p 6), or rifampicin plus dapsone plus clofazimine (see comment on multidrug treatment for multibacillary leprosy, p 5).

Clinical guide:
Single dose treatment has operational advantages in the field, particularly when people live in remote areas and are unable to attend a clinic for several months. [33]

GLOSSARY

Bacteriological index A measure of the density of *Mycobacterium leprae* in the skin. Slit skin smears are made at several sites, and the smears are stained and examined microscopically. The number of bacteria per high power field is scored on a logarithmic scale (0–6), and the index calculated by dividing the total score by the numbers of sites sampled.
ICRC vaccine A vaccine developed at the Indian Cancer Research Centre.
Multibacillary leprosy More than five skin lesions. [34]
Neuritis Inflammation of a nerve, presenting with any of the following: spontaneous nerve pain, paraesthesia, tenderness, or sensory, motor, or autonomic impairment.
Paucibacillary leprosy Between two and five skin lesions.

Person years at risk The number of new cases of disease in a specified time period divided by the number of person years at risk during that period (average number at risk of relapse multiplied by the length of observation).
Ridley–Jopling classification of people with leprosy This scale classifies people with leprosy according to their clinical features and bacterial load which reflect their immune response to *Mycobacterium leprae*. The scale forms a spectrum of people with tuberculoid leprosy (TT) and high cell mediated immunity at one pole. These people have just one skin or nerve lesion. At the other pole is lepromatous leprosy (LL) with no cell mediated immunity for *M leprae* and widespread disease with skin nodules and multiple nerve involvement. In between these poles are the borderline forms (Borderline tuberculoid [BT], Borderline [BB], and borderline lepromatous [BL]) which have intermediate clinical and immunological forms. The complete spectrum consists of TT, BT, BB, BL, and LL. Histopathological examination of skin lesions is often useful in confirming the classification.
Single lesion leprosy One skin lesion.
Type 1 (reversal) reaction A delayed type hypersensitivity reaction occurring at sites of *Mycobacterium leprae* antigen. It presents with acutely inflamed skin lesions and acute neuritis (nerve tenderness with loss of function).
Type 2 reaction or erythema nodosum leprosum An immunological complication of multibacillary leprosy presenting with short lived and recurrent crops of tender erythematous subcutaneous nodules that may ulcerate. There may be signs of systemic involvement with fever, and inflammation in lymph nodes, nerves, eyes, joints, testes, fingers, toes, or other organs.
World Health Organization disability grading A simple grading system for use in the field, mainly for collection of general data regarding disabilities. [1] Grade 0 = no anaesthesia, no visible deformity or damage; grade 1 = anaesthesia present, but no visible deformity or damage; grade 2 = visible deformity or damage present.
High-quality evidence Further research is very unlikely to change our confidence in the estimate of effect
Low-quality evidence Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Very low-quality evidence Any estimate of effect is very uncertain

SUBSTANTIVE CHANGES

Bacillus Calmette Guerin versus no treatment or placebo One systematic review added; [12] benefits data added, but categorisation unchanged (Beneficial).
Mycobacterium w vaccine versus placebo One RCT added; [17] benefits and harms data added, but categorisation unchanged (Unlikely to be beneficial).

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TABLE 1 **BCG vaccines against leprosy.**

Ref	Location	Cohort size (age range in years)	Intervention *v* comparison	Follow up (years)	New cases of leprosy
[35]	Uganda	19 323 (0 16)	BCG *v* no treatment	14	143/9036 (1.6%) *v* 19/9052 (0.2%); ARR 1.4%; NNT 73, 95% CI 69 to 80
[36]	Myanmar (formerly Burma)	14 435 (0 14)	BCG (one containing a concentration of viable bacilli acceptable to WHO , the other a higher concentration) *v* no treatment	13 16	Lower (WHO) concentration: 5.0/1000 person years with BCG *v* 5.6/1000 person years; RRR 11%, 95% CI 3% to 23% Higher concentration: 3.8/1000 person years with BCG *v* 5.4/1000 person years for controls; RRR 30%, 95% CI 19% to 40%
[37]	Papua New Guinea	5356 (48% < 14; 52% less-than or equal to 15)	BCG *v* saline	13 16	2.8 per 1000 person years with BCG *v* 5.4 per 1000 person years with saline; RRR 48%, 95% CI 34% to 59% (absolute numbers not available)
[38]	India	290 000 (1 65)	BCG (38 213 people); normal saline (38 697 people)	6 7	BCG *v* saline, RRR 34.1%, 95% CI 13.5% to 49.8% (absolute numbers not available)
[39]	Malawi	121 020 (0.25 75) With a BCG scar: 54 685 Without a BCG scar: 61 155	BCG or BCG plus killed *M leprae v* placebo (54 865 scar positive people)	5 9	RR 0.51, 95% CI 0.26 to 0.99
[39]	Malawi	See above	BCG plus killed *M leprae v* BCG (66 155 scar negative people)	5 9	RR 1.06, 95% CI 0.62 to 1.82
[38]	India	See above	BCG plus killed *M leprae* (38 229 people) Saline (38 697 people)	2 4 6 7	RRR 64.0%, 95% CI 50.4% to 73.9% (absolute numbers not available)
[38]	India	See above	ICRC (22 541 people) Saline (38 697 people)	2 4 6 7	RRR 65.5%, 95% CI 48.0% to 77.0% (absolute numbers not available)
[38]	India	See above	*Mycobacterium w* (33 720 people) Saline (38 697 people)	2 4 6 7	RRR 25.7%, 95% CI 1.9% to 43.8% (absolute numbers not available)

BCG, Bacillus Calmette-Guerin; WHO, World Health Organization

TABLE 2 **Vaccines against leprosy.** [1] [2] [3]

Ref	Location	Cohort size (age range in years)	Intervention comparison	Follow up (years)	New cases of leprosy
[13]	India	290 000 (1–65)	BCG (38 213 people) *v* normal saline (38 697 people)	6–7	BCG *v* saline, RRR 34.1%, 95% CI 13.5% to 49.8%; absolute numbers not available
[15]	Malawi	121 020 (0.25–75) With a BCG scar: 54 685 Without a BCG scar: 61 155	BCG or BCG plus killed *M leprae v* placebo (54 865 scar positive people)	5–9	RR 0.51, 95% CI 0.26 to 0.99
			BCG plus killed *M leprae v* BCG (66 155 scar negative people)	5–9	RR 1.06, 95% CI 0.62 to 1.82
[17]	India	290 000 (1–65)	BCG plus killed *M leprae* (38 229 people) *v* saline (38 697 people)	2–4 6–7	RRR 64.0%, 95% CI 50.4% to 73.9%; absolute numbers not available
			ICRC (22 541 people) *v* saline (38 697 people)	2–4 6–7	RRR 65.5%, 95% CI 48.0% to 77.0%; absolute numbers not available
			Mycobacterium w (33 720 people) *v* saline (38 697 people)	2–4 6–7	RRR 25.7%, 95% CI 1.9% to 43.8%; absolute numbers not available
[3]	India	24 060 household contacts of patients with leprosy enrolled	*Mycobacterium w* vaccination of patients and contacts *v* placebo for both	3–4 6–8 9–10	ORR 68%, 95% CI 42% to 83% ORR 60%, 95% CI 39% to 72% ORR 28%, 95% CI 5% to 45%
			Mycobacterium w vaccination of contacts only *v* placebo for both	3–4 6–8 9–10	ORR 69%, P = 0.00006 (CI values incorrectly reported) ORR 59%, 95% CI 38% to 72% ORR 39%, 95% CI 20% to 54%
			Mycobacterium w vaccination of patients only *v* placebo for both	3–4 6–8 9–10	ORR 43%, 95% CI 7% to 65% ORR 31%, 95% CI 3% to 50% ORR +3%, 95% CI –24% to +25%

BCG, Bacillus Calmette-Guerin; WHO, World Health Organization.

TABLE 3 **Case series of dapsone plus rifampicin plus clofazimine in multibacillary leprosy: clinical outcomes and relapse rates.** [18] [19] [20] [21] [22] [23]

				Clinical outcome		
Ref	**Location**	**Participants**	**Follow up (years)**	**Skin lesions**	**Nerve impairment**	**Relapse rates**
[18]	Thailand	53	Range 10–12	Clinically active at about 3 years: 14/49 (29%)	Grade 2 disability: Start of treatment: 8% End of treatment: 13%	0/1000 PYAR
[19]	Ethiopia	256 (57 people with BI > 4 at enrolment)	4.3 (range 0–8.6); 38% followed up for greater-than or equal to 5 years	No data	No data	0/1000 PYAR
[20]	Thailand	220	3	No data	No data	2/198 (1.0%) 3.3/1000 PYAR
[21]	China	2318	10	No data	No data	0/1000 PYAR
[22]	India	260	Range 1–8	No data	No data	20/260 (7.7%) 20.4/1000 PYAR 18/20 (90%) with BI > 4 at enrolment
[23]	India	65	Range 1–8	No data	No data	1/46 (2.1%) 0.023/1000 PYAR

BI, bacterial index, PYAR, person years at risk; Ref, reference.

TABLE **GRADE evaluation of interventions for leprosy**

Important outcomes	**Incidence of leprosy, mortality, clinical improvement, adverse effects**								
Number of studies (participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
What are the effects of interventions to prevent leprosy?									
27 studies (at least 38,213 people) [12] [13] [14]	Incidence of leprosy	BCG vaccine *v* placebo	4	–1	–1	0	0	Low	Quality point deducted for inclusion of non-randomised studies. Consistency point deducted for heterogeneity between studies
1 (5356) [14]	Mortality	BCG vaccine *v* placebo	2	0	0	0	0	Very low	
2 (93,094) [15]	Incidence of leprosy	BCG vaccine plus killed *M leprae v* placebo	4	0	0	–1	+1	High	Directness point deducted for multiple interventions in comparison. Effect size point added for RR less than 0.5
1 (121,020)	Incidence of leprosy	BCG vaccine *v M leprae* vaccine	4	0	0	–1	0	Moderate	Directness point deducted for multiple interventions in comparison
1 (22,541) [13]	Incidence of leprosy	ICRC vaccine *v* placebo	4	0	0	0	+1	High	Effect size point added for RR less than 0.5
2 (63,140) [17]	Incidence of leprosy	*Mycobacterium w* vaccine *v* placebo	4	0	0	0	0	High	
2 (at least 121,020) [15] [16]	Incidence of leprosy	Higher concentration BCG vaccine *v* lower concentration BCG vaccine	4	–2	–1	0	0	Very low	Quality point deducted for inclusion of nonrandomised study, and other methodological flaws. Consistency point deducted for conflicting results.
What are the effects of treatments for leprosy?									
1 (1483) [32]	Marked clinical improvement	Single-dose antibiotics *v* multiple dose antibiotics	4	–2	0	0	0	Low	Quality points deducted for diagnostic uncertainty and short follow-up

Type of evidence: 4 = RCT; 2 = Observational; 1 = Non-analytical/expert opinion. Consistency: similarity of results across studies. Directness: generalisability of population or outcomes.